Time to Take the Failure out of Heart Failure: The Importance of Optimism.

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"It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so" Mark Twain

Most patients with heart disease develop heart failure before they die (1). Medical articles usually portray heart failure as a disease that follows an inexorable downhill course unless suddenly interrupted by a fatal arrhythmia. This doom-laden narrative is usually reinforced by a series of "mantra" cut-and-pasted with little thought from a handful of original articles; "5.7 million Americans have heart failure" (defined exactly how and does no other nationality matter?); "the annual cost of heart failure is >$30 billion" (to whom?); "five-year survival is dismal" (for all patients and compared to what?); "morbidity and mortality remain unacceptably high" (exactly what would be acceptable?). Is this depressing depiction of heart failure really true, or has it become true only through frequent repetition and uncritical acceptance of received wisdom? Perhaps there might be a benefit in encouraging each other to be more optimistic for our patients? Who would want to invest (public) money in a lost cause; who would invest in failure? Patients are potentially the greatest resource (civil, political and medical) for improving healthcare but it is difficult to ask for a patient's help if the doctor or nurse appear as harbingers of doom. Doctors must distinguish the "spin" of the lobbyists who believe that a message of fear and failure will obtain more resources for research and care from the clinical facts, which are not the same for all patients. Without facts how can we inform patients properly and consequently ensure that joint decisions in care are optimal. We require data and its correct interpretation. Time now to re-examine some of the shibboleths of heart failure.

In this edition of JACC-Heart Failure, Kalogeropoulos AP and colleagues provide us with some granular data, describing the incidence of progression from chronic stable (Stage C) to advanced (Stage D) heart failure in a substantial cohort of patients with a reduced left ventricular ejection fraction (HFrEF) in a high-quality academic health care system; Emory Health Care (2). There is no agreed definition of Stage D. In this report, it was based on medical judgement and/or the need for desperate measures (eg:- heart transplantation, left ventricular assist device (LVAD), inotropic therapy or palliative care). Many more patients might have been deemed to have progressed had another definition been used, such as recurrent hospitalization for heart failure. Age and co-morbidity may influence the use of treatments for advanced heart failure and therefore the nature of the patients reaching this endpoint.

Why is this analysis important? Most pharmacological treatments for patients with chronic stable heart failure are generic and low-cost although many patients with HFrEF will require an implanted electrical device, which have substantial acquisition and maintenance costs. Most of the other costs of managing heart failure arise due to the inability to control congestion adequately resulting in hospitalization. The importance of "Stage D" is that it reflects intractable or recurrent congestion that is debilitating for patients and costly for health services. Controlling congestion and preventing sudden death are key therapeutic goals in the management of heart failure; indeed, poorly controlled congestion may be an important trigger for ventricular and supra-ventricular arrhythmias and sudden death.

In the Emory cohort, the average patient age was 62 years, similar to that observed in many clinical trials but about 15 years younger than the epidemiological average. Many patients

were in New York Heart Association class III or IV at baseline and might have already been in Stage D. Younger age or referral patterns might account for the low rate of some co-morbidities. Most patients were treated with ACE inhibitors and beta-blockers at the time of evaluation but only half of the patients had an implantable defibrillator. Presumably utilization of guideline-recommended therapies increased after initial patient-evaluation under the aegis of an expert health care system. Within three years about 25% of patients had died or progressed to Stage D; about 9% per year. This is remarkably similar to the rate of the primary outcome observed in the PARADIGM *(Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor]with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure)* trial for patients with chronic stable heart failure assigned to sacubitril/valsartan. In the Emory cohort, the annual rate of progression to Stage D was 4.5% (but perhaps 6% if some grey-cases were included). Overall between 112 and 154 of 964 patients in this cohort progressed to Stage D over three years but only 21 of these received an LVAD and only seven a heart transplant. However, death prevented the possibility of reaching Stage D in a further 4.7% patients each year. Presumably most of these deaths were sudden, although some may have been non-cardiovascular. More African-American patients progressed to Stage D but this may be because they were less likely to die before progressing. Progression to Stage D is, in some senses, good news because it is potentially reversible, unlike death. Prediction models for non-fatal outcomes in populations with a high mortality must be interpreted with extreme caution because there are two ways to prevent non-fatal events, only one of which is good news. Death may pre-empt progression or progression may be prevented by an effective therapeutic package. This is a major limitation of the risk-score presented in this paper.

Treatment with either beta-blockers or ACE inhibitors was strongly associated with lower mortality before reaching Stage D but not with progression to Stage D. This is best explained by a reduction in sudden death, since these agents are not known to reduce non-cardiovascular mortality, due to or combined with a reduction in disease progression (3). Treatments that reduce sudden death but do not delay disease, as might be expected with an implantable defibrillator, may increase the number of patients in stage D and therefore the costs of healthcare. However, in the Emory cohort, implantable defibrillators were neither associated with a lower mortality prior to reaching stage D nor an increase in patients progressing to Stage D. Perhaps patients with implanted devices were at lower risk (younger age or milder symptoms) or had better pharmacological treatment. However, it is possible that sophisticated statistical analysis has disguised rather than illustrated the effect of treatment on outcomes. Simpler reporting of data is often better. Statistical models show only associations which often reflect variables that are surrogates for the true drivers of outcomes. Multivariable analyses should always be supported by expert clinical interpretation of an accompanying univariate analysis. Also, data-driven models should be compared to models based on clinical selection of key prognostic markers.

Publishing from the same data-set, Kalogeropoulos AP and colleagues previously reported that 16.2% of patients with HFrEF had recovery of their left ventricular ejection fraction (LVEF) (4). The mortality at 3 years amongst these patients was 4.8% compared to 13.2% amongst those patients whose LVEF had not recovered. This is an important message corroborated by other reports. For instance, for patients aged <67 years randomized to cardiac resynchronization therapy in the CARE-HF (Cardiac Resynchronization – Heart Failure) study (New York Heart Association (NYHA) class III/IV heart failure with LVEF <35%), more than half were still alive 10 years later; many in NYHA class II (5). This much more

optimistic scenario is surely more appealing to patients, their advocacy groups, health professionals and research funders alike.

In summary, Kalogeropoulos AP and colleagues have provided interesting analyses that provide new insights both into the progression of heart failure and its recovery. More trials are required to show that interventions such as inotropic therapy and LVADs lead to worthwhile improvements in wellbeing and outcome compared to expert pharmacological therapy in patients who have progressed to Stage D. However, it is strategically important that the heart failure community works harder on public relations; putting more emphasis on success and less on failure. Let's dispel the narrative of gloom and doom.

"Nothing succeeds like success" Sir Arthur Helps

Legend to Figure

Title:- Forecast for Patients Age <70 years with Stable HFrEF in 2017.

Blue arrows indicate current expectations for a patient aged <70 years with stable heart failure and mild-to-moderate symptoms managed in a good-quality, well-resourced cardiology service. Red crosses reflect the twin goals of preventing sudden death and disease progression. The red arrows represent the twin goals of reversing disease progression and increasing recovery after stabilization.

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Forecast for Patients Age <70 years with Stable HFrEF in 2017